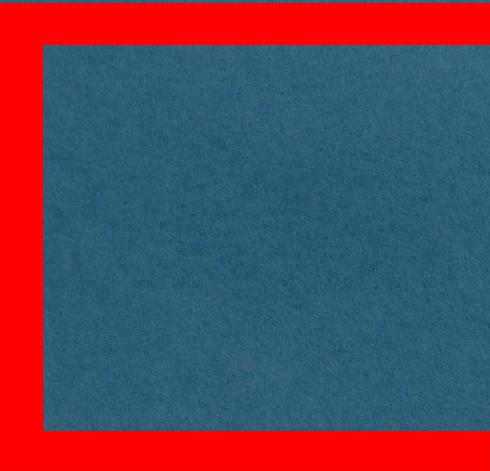




FDA Inspections: The Warrantless Search



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Today's Agenda

- The Warrantless Search:
 - What is the FDA inspecting?
 - What is the FDA looking for?
 - What are they allowed to request?
 - Plain sight?
 - Photos?

Related Topics

- Current Good Manufacturing Practices (cGMP)
- Adulteration and Misbranding
- Statutes that Authorize Inspections
- Types of inspections: foreign, domestic inspections and Sections of the FDCA that Authorize Inspections
- Elements of the Form 483
- Observations
- Consequences: Warning Letters and Enforcement Actions
- FDA Enforcement Options and Authority

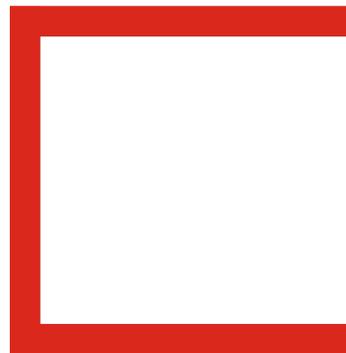
What is the FDA Looking for?

- Compliance with GMP (cGMP's)
- Proper Registration and Licensing
- Documentation especially Improper or lacking documentation
- Proper manufacturing
- Complaints
- Investigations
- Out of Specification (Lab)
- Deviations (Manufacturing)
- Organizations Structure (Especially QA)
- Qualifications of the Personnel
- Proper Training

What are they really looking for?

- Intent (to do the right thing or not)
- Bad Actors
- Short cuts
- Sloppy work
- Inadequate documentation
- & more...

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Definitions & Legal Citations

Adulterated Drugs

Adulterated Drugs (21 U.S.C § 351)

A drug is considered adulterated if:

- contains any filthy or decomposed substance
 - (FDCA §501(a)(1), 21 U.S.C. §351(a)(1));
- prepared, packed or held under unsanitary conditions
 - (FDCA §501(a)(2)(A), 21 U.S.C. §351(a)(2)(A));
- **methods or processes used are not in conformance with good manufacturing practices**
 - **(FDCA §501 (a)(2), 21 U.S.C. §351 (a)(2)(b), 21 CFR Part 210 & 211);**
- container composed of poisonous or deleterious substance may cause contents to be injurious to health
 - (FDCA §501 (a)(3), 21 U.S.C. §351 (a)(3));
- contains an unsafe coloring additive
 - (§501 (a)(4), 21 U.S.C. §351 (a)(4));
- strength, quality or purity falls below compendia standards
 - (§501 (b), 21 U.S.C. §351 (b));
- strength or purity falls below what it purports to possess
 - (§501 (c), 21 U.S.C. §351 (c));
- mixed or packaged to reduce quality or strength
 - (§501 (d), 21 U.S.C. §351 (d)).



Misbranding (21 USC § 331)

- labeling is false or misleading
 - (FDCA §502 a), 21 U.S.C. §352(a));
- label fails to bear the name and place of business, an accurate statement of contents, weight, measure or numerical count
 - (FDCA §502(b), 21 U.S.C. §352(b));
- labeling required is not prominently displayed and understandable
 - (FDCA §502(c), 21 U.S.C. §352(c));

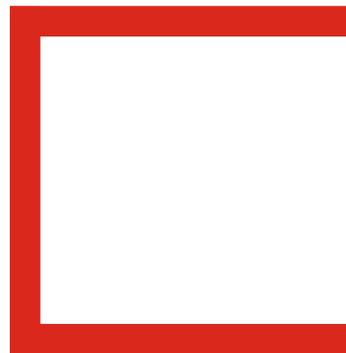
Good Manufacturing Practice (GMP)

- Good manufacturing Practices were implemented by the FDA to ensure that Drug Products are manufactured in an appropriate and safe way
 - (21 CFR 210 & 211)
- FDCA grants FDA authority to ensure compliance with current GMP
 - (cGMP) (§ § 301(a), 501(a)(2)(b); 21 USC § § 331(a); 351(a)(2)(b))
- A Drug is adulterated if found not to be manufactured according to cGMP's
 - (§ § 301(a), 501(a)(2)(b));

Good Manufacturing Practice (GMP)

- **A drug can meet its specifications, contain no detectable impurities, be both safe and effective and still be considered adulterated if the manufacturing was not in compliance with cGMP's.**
 - (FDCA §501 (a)(2), 21 U.S.C. §351 (a)(2)(b), 21 CFR Part 210 & 211);
- Quality should be built into the product and testing alone cannot be relied upon to ensure product quality”
 - (FDA Guidance for Industry, Sept. 2006)

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The Inspection

The Investigators Arrive

Hi We're from the Government and we're here to help?

Hi We're from the government and we are here to help!

What do we do now?

Maybe not?

Inspection Parameters

- Credentials and Notice of Inspection Form 482
- Only Entitled to Statutorily Mandated Information
 - Company must know what is statutorily mandated
 - Inspectors often ask for more info
 - If provided has been “voluntarily granted with company’s consent”

Inspections

- Reasonableness of the Inspection (time, limits, manner) § 704
- Frequency of Inspections 21 U.S.C. §360(h)
- No Consent is Required (Pervasively and Extensively regulated industry)
- No Search Warrant is Required
- Miranda Warnings do not apply unless criminal investigation is opened (none for Inspection and evidence admissible criminally)
- Administration Inspection Warrants

Inspection Parameters

FDA entitled to:

- Relevant information concerning whether drugs (for human consumption) are:
 - Manufactured
 - Transported
 - Processed
 - Packed
- In accordance with the Act [FDCA]
- (704(a)(1); 21 USC 374(a)(1))

Inspection Parameters

Not entitled to:

- Financial Data
- Sales Data (other than shipping amounts, Units)
- Pricing data
- Personnel data (other than the qualifications of professional personnel)
- Research data (except for data required to be disclosed under 21 USC 374 'approval data')
- Internal audit, supplier audit, mgmt reviews)

Inspection Parameters

May attempt to obtain:

- Not statutorily or regulation authorized
 - Affidavits from individuals (**NEVER sign**)
 - Interview of employees (**only those you select**)
 - FDCA does not authorize investigators to interview a company's employees; (**if so, with counsel present**)
 - Managerial or non-managerial employees

Good Manufacturing Practice (GMP)

GMP's: Ten (10) Sections:

- Organization and Personnel
- Buildings and Facilities
- Equipment
- Components, Drug Product Containers, and Closures
- Production and Process Control
- Packaging and Labeling Control
- Holding and Distribution
- Laboratory Controls
- Records and Reports
- Returned Drug Products

Inspection Types

- An establishment inspection is a careful, critical, official examination of a facility to determine its compliance with laws administered by FDA.
- ***Inspections may be used to obtain evidence to support legal action when violations of the law are found*** or they may be directed to obtain information on new technologies, good commercial practices or data for establishing other regulations, etc.

Inspections

Authority:

- Domestic Inspections Section 704 or 21 U.S.C. §374; 21 U.S.C. §360(h)
- Foreign Inspections authority Section 801 of the Act and commitments made by the sponsors of applications, if applicable.
- **For that reason, the agency is not required to provide stringent documentary evidence to establish violations of the Act.**

Inspection Parameters

Routine inspections every two years

More often for:

- Follow-up to Warning Letter
- Enforcement action (Consent Decree, etc.)
- Response to complaints
 - (consumers/healthcare professionals/employees)
 - Special issues: serious adverse events reported

Inspection Parameters

- “Reasonable time” when regulated activities are being conducted (“normal business hours”)
 - (U.S. v. New England Grocers Supply Company, 488 F.Supp. 230, 239 (D. Mass 1980))
- and “reasonable manner” still being defined by courts
 - (i.e. photo’s, manual v. Dow Chem)

Inspection Parameters

- “each inspection shall be commenced and completed with with reasonable promptness”
 - (704(a)(1); 21 USC 374(a)(1))
- In reality several days to three weeks
- Initiation and Conducting the Inspections (bolts and nuts perspective; breakout session)

Inspection Conclusions

Form 483

- Observations on:
 - Unsatisfactory conditions
 - Actual violation of cGMP
 - Potential violation of cGMP (usually not noted but verbally stated)
 - 483's issued in over 60% of all inspections (now closer to 80%)
 - No 483 issued, Company "passed inspection"

Inspection Conclusions

- Post inspection discussion with investigators (optional)
- Usually helpful to figure out FDA next steps
- Corrective actions disclosed
- Review of Form 483

Establishment Inspection Report

- More detail description of 483 observations
- Generally tracks and expands on 483
- Classifies as “Voluntary Action Indicated” or “VAI” or “Official Action Indicated” or “OAI”
- OAI usually indicates enforcement action of some type (Warning Letter, etc.)

Establishment Inspection Report

- “RTS” Referred to State, local, or other federal office.
 - no federal jurisdiction over violation
 - state action is the least involved and fastest
- “RTC” or Referred to Center
 - No clear policy
 - technical issues require Center review

Foreign Inspections

- FDA routinely completes inspections of foreign facilities with API or finished drug product headed for import into U.S.
- Usually scheduled several weeks in advance (unlike impromptu domestic inspections)
- Voluntary---sanctions if refused:
 - Prevent importation of drugs
 - Withhold drug approvals

GMP: Proof in Litigation

- FDA must only prove :
 - Manufacturer did not follow a particular practice
 - Practice was deemed “Good” by FDA
- Cases:
 - Provide flexibility...specific enough to assure drug is safe and reliable...
 - U.S. v. Bel Mar Labs, 284 F. Supp. 875

Warning Letters

■ What

- Letter regarding violations documented during inspections or investigations
- Issued only for violations of “regulatory significance”

■ When

- Significant violation and reasonable prospect that warning will result in correction
- No bluffing
- Prior warning not required
- Goal is voluntary compliance.
- No warning if conduct is intentional or threatens public safety

Criminal Prosecutions

Important Distinctions in Criminal Cases

- **The FDCA is a strict liability statute (very rare)**
 - **An individual may be found guilty of an FDCA misdemeanor violation even though:**
 - He did not intend to violate the law;
 - He did not actively participate in the violation; and/or
 - He did not act negligently
 - **Under the Supreme Court's decision in United States v. Park, it is enough that a corporate executive had the power and duty to prevent a violation and that he failed to do so**

FDA Enforcement Authority

- Remedies to protect the public, punish violators, and deter violations
 - Administrative: warning/untitled letters, product recalls, civil penalties, debarment, withdrawals of product approvals
 - Judicial: certain civil penalties, seizures, injunctions, criminal prosecutions
 - All FDA court cases are filed by DOJ under the name of the United States
 - Informal: publicity, cooperation with other governmental entities

Inspections

- **Often precede enforcement action**
- **Findings form basis for many enforcement actions**
- **15-day post-inspection deadline to respond**
 - Commissioner Hamburg: “Once the FDA provides inspection findings identifying a serious problem, the firm will generally have no more than 15 working days in which to respond before the FDA moves ahead with a Warning Letter or enforcement action.”
- **48-hour deadline in some circumstances**
 - See FDA Press Release: **FDA Warns Web Sites against Marketing Fraudulent H1N1 Flu Virus Claims**, available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm166801.htm>

Enforcement Tactics By Product Type

	Prosecution	Injunction	Seizure	Civil Money Penalties ⁴	Mandatory Recall	Voluntary Recall	Warning Letter	Administrative Detention
Biologics ¹	X	X		X	X	X	X	
Cosmetics	X	X	X			X	X	
Devices	X	X	X	X	X	X	X	X
Drugs (Animal)	X	X	X			X	X	
Drugs (Human)	X	X	X	X		X	X	
Food (Animal)	X	X	X			X	X	X
Food (Human) (including Dietary Supplements)	X	X	X	X		X	X	X
Infant Formula ²	X	X	X		X	X	X	
Electronic Products ³	X	X		X	X	X	X	
Vectors of Communicable Disease	X	X				X	X	

¹ Biologics are also drugs and, in some cases, devices - see human drug and device tools.

² Infant Formula is also food - see human food tools

³ Some electronic products are also devices - see device tools

⁴ In limited circumstances

Enforcement Tactics By Product Type

	Debarment	Clinical Investigator/ IRB Disqualification	Imports - Refusal of Admission	361 Order ¹	Suspension	Withdrawal of Approval	Publicity	Intergovernmental Cooperation
Biologics		X			X	X	X	X
Cosmetics							X	X
Devices	X	X	X		X ²	X ²	X	X
Drugs (Animal)		X	X		X	X	X	X
Drugs (Human)	X	X	X		X	X	X	X
Food (Animal)	X		X			X ³	X	X
Food (Human) (including Dietary Supplements)	X		X			X ³	X	X
Infant Formula							X	X
Electronic Products							X	X
Vectors of Communicable Disease				X			X	X

¹ Can apply to all types of products or other vectors of communicable disease ² Devices approved under PMA's ³ Food Additives only

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Biologics ¹	X	X		X	X	X	X	
Cosmetics	X	X	X			X	X	
Devices	X	X	X	X	X	X	X	X
Drugs (Animal)	X	X	X			X	X	
Drugs (Human)	X	X	X	X		X	X	
Food (Animal)	X	X	X			X	X	X
Food (Human) (including Dietary Supplements)	X	X	X	X		X	X	X
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Electronic Products ³	X	X		X	X	X	X	
Vectors of Communicable Disease	X	X				X	X	

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Thank you

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